

SECTION 4: GLYCEMIC CONTROL

Concern	Care/Test	Frequency
Glycemic Control	♦ Check A1c (see Algorithm 1).....	<i>Type 1:</i> Every 3 months
	Goal: < 7.0% or ≤ 1% above lab norms	<i>Type 2:</i> Every 3 – 6 months
	♦ Review goals, meds, side effects, and frequency of hypoglycemia	Each focused visit
	♦ Assess self-blood glucose monitoring schedule.....	Each focused visit, 2 – 4 times/day, or as recommended

The American Diabetes Association (ADA) recommends an A1c < 7%. Good glycemic control is cost-effective and improves quality of life. It is estimated that for every one percent decrease in A1c, there is a 14-20% decrease in hospitalizations, resulting in \$4-5 billion savings in direct health care costs alone.

Optimal treatment should be offered to all people with diabetes. Glycemic goals should be achievable, realistic, and individualized for every person. Goals may need to be adjusted according to the person's age (i.e., children and the elderly), severity and/or frequency of hypoglycemia, hypoglycemic unawareness, lifestyle factors, comorbid conditions, self-management skills, and motivation. The person with diabetes, his/her family, and the health care providers should agree upon all goals.

Table 5: Wisconsin Guidelines for Glycemic Control

Biochemical Index	Normal	Goal	Initiation of Action Suggested
Average Fasting Plasma Glucose (mg/dL) pre-prandial or pre-meal	< 100	90 – 130	< 80 or > 140
Average 2 hour (mg/dL) post-prandial or post-meal	< 140	< 180	> 180
Average Bedtime Glucose (mg/dL)	< 120	110 – 150	< 110 or > 160
A1c (%) Sustained	< 6%	< 7%	≥ 7%

Notes:

- Individual circumstances may warrant different treatment goals.
- Laboratory methods measure plasma glucose.
- Normal values for A1c may vary from lab to lab.
- Meter and lab correlation may vary by 10-20%.
- It is important for people with diabetes to know whether their meters and strips record whole blood or plasma results; most glucose monitors approved for home are plasma results.
- These values are for non-pregnant women.

A1c

The A1c test has become the gold standard for assessing and monitoring glycemic control in people with diabetes. The percentages of A1c values are correlated to the average blood glucose control over the last 60-90 days (see Table 6). The ADA recommends testing a minimum of two times per year depending on the clinical situation, type of treatment, and the judgment of the clinician. A1c values can vary in different laboratories and adjustments should be made to take into account local differences in assay methodology and non-diabetic reference ranges.

Table 6: Correlation of A1c Level and Average Whole Blood and Plasma Glucose Levels

A1c (%)	Average Whole Blood Glucose (mg/dL)	Average Plasma Glucose (mg/dL)
6	120	135
7	150	170
8	180	205
9	210	240
10	240	275
11	270	310
12	300	345
13	330	380
14	360	415

Accuracy of A1c

There are several conditions that may affect the accuracy of A1c. Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (i.e., recovery from acute blood loss, hemolytic anemia) falsely lowers A1c test results. Other medical conditions, such as kidney and liver disease, may also falsely lower the A1c measurement. Additionally, a variety of hemoglobin disorders can interfere with A1c assay methods, independent of shortened erythrocyte survival. Depending on the particular hemoglobinopathy, the A1c test results can be either falsely increased or decreased. Non-hemoglobin based methods for assessing long-term glycemic control, such as a fructosamine test, may be useful in these situations.

Self-Monitoring of Blood Glucose

Self-monitoring of blood glucose (SMBG) is a powerful tool that allows people the opportunity to know exactly what their blood glucose level is at any time of day. This information can be used to enhance self-management skills and guide additional lifestyle changes and medical treatment. All people with diabetes benefit from SMBG. It is important for health care providers to evaluate each person's monitoring technique for accuracy initially and at regular intervals thereafter. Providers can reinforce monitoring and review blood glucose logs during diabetes-focused visits. Most blood glucose monitors approved for home use are now calibrating blood glucose readings to plasma glucose levels. Older monitors (e.g., One Touch Profile) still measure whole blood glucose levels. Plasma glucose values are 10-15% higher than whole blood values. It is critical that people know whether their monitor provides whole blood or plasma glucose levels.

Optimal use of SMBG requires interpretation of data with the goal of making adjustments to food intake, physical activity, or pharmacological therapy. Blood glucose test results will vary considerably; therefore high numbers must not always be interpreted as person being non-compliant or doing poorly. People can learn how to interpret home blood glucose data to further modify lifestyle changes. Providers should review home blood glucose logs, as many times this data can be used to modify treatment regimens to optimize glycemic control.

Monitoring blood glucose can be difficult, expensive, and time-consuming. Providers can encourage people to talk about personal goals and/or assist them by offering strategies to help individuals improve their SMBG skills.

Frequency and timing of SMBG testing is very dependent on each person's condition, individual circumstances, and/or need. Multiple testing schedules are possible and each must be individualized (see Table 7). The following circumstances may factor into the frequency for SMBG testing recommendations:

- Type of diabetes
- Blood sugar fluctuation
- Type of treatment (e.g., oral medication, insulin, diet, and physical activity)
- Recent adjustments to medications/insulin
- Stress
- Affordability of supplies needed

Table 7: Self-Monitoring of Blood Glucose Suggestions

Condition	Testing Amount	Comment
Type 1: controlled with insulin injections (intensive regimens, multiple injections, or pump)	<u>4 to 6 times/day or more</u> (anytime there is risk of low, if person feels low, and/or prior to driving)	<ul style="list-style-type: none"> ♦ Fasting, pre-meal, and bedtime ♦ 2 hour post-meal is beneficial especially when trying to achieve tighter control by adjusting insulin for the specific grams of carbohydrates consumed before a meal
Type 2: controlled with insulin (intensive regimens, multiple injections, or pump)	<u>2 to 4 times/day or more</u> (anytime there is risk of low, if person feels low, and/or prior to driving)	<ul style="list-style-type: none"> ♦ Fasting, pre-meal, and bedtime (rotate schedule by using 2 times/day) ♦ 2 hour post-meal is beneficial especially when trying to achieve tighter control by adjusting insulin for the specific grams of carbohydrates consumed before a meal
Type 1 & 2: when adding to, or modifying, therapy	<u>4 times/day or more</u> (anytime there is risk of low, if person feels low, and/or prior to driving)	<ul style="list-style-type: none"> ♦ Fasting, pre-meal, bedtime, and/or 2 hour post-meal ♦ 2 hour post-meal is beneficial especially when trying to achieve tighter control by adjusting insulin for the specific grams of carbohydrates consumed before a meal
Type 1 & 2: during illness (if taking insulin and oral medications)	<u>4 times/day or more</u> (urine or blood ketones test with each blood sugar > 250 mg/dL)	<ul style="list-style-type: none"> ♦ Fasting, pre-meal, and bedtime ♦ 2 hour post-meal is beneficial especially when trying to achieve tighter control by adjusting insulin for the specific grams of carbohydrates consumed before a meal
Type 2: controlled with diet and physical activity and/or oral medications	<u>1 to 4 times/day or more</u> (anytime there is risk of low, if person feels low, and/or prior to driving)	<ul style="list-style-type: none"> ♦ Fasting, pre-meal, bedtime, and/or 2 hour post-meal (alternate days with varied time) ♦ 2 hour post-meal is beneficial especially when trying to achieve tighter control by adjusting insulin for the specific grams of carbohydrates consumed before a meal
Pre-conception	<u>4 to 6 times/day or more</u> (anytime there is risk of low, if person feels low and/or prior to driving)	<ul style="list-style-type: none"> ♦ Fasting, pre-meal, and bedtime ♦ 2 hour post-meal is beneficial especially when trying to achieve tighter control by adjusting insulin for the specific grams of carbohydrates consumed before a meal
Pregnancy	<u>4 to 6 times/day or more</u> (anytime there is risk of low, if person feels low, and/or prior to driving)	<ul style="list-style-type: none"> ♦ Fasting and 2 hour post-meal

These testing schedules and recommendations are intended to serve as a guide for health care providers. They are not intended to replace or preclude clinical judgement.

Oral Hypoglycemic Agents

Therapeutic treatment options for diabetes have greatly expanded in recent years. Treatment options that reduce fasting plasma glucose (FPG) and A1c include Sulfonylureas, Biguanides, Meglitinides, Alpha Glucosidase Inhibitors, Thiazolidinediones, and Insulin Analogs.

Scientific evidence clearly indicates that improved glycemic control and treating-to-target are cost-effective and improve quality of life. Intensifying pharmacological treatments using newer therapies can help providers achieve optimal glycemic control whenever A1c is $\geq 7.0\%$, or when individual goals and daily blood sugar monitoring are not showing a pattern of improvement.

Lifestyle changes, education, and SMBG are the chief cornerstones of therapy and should be maintained throughout all steps of treatment for people with Type 1 and Type 2 diabetes. If a person with Type 2 diabetes is making lifestyle changes (diet and physical activity) and is unable to achieve normal or near normal glucose levels despite adequate education and personal effort, pharmacological treatment with oral hypoglycemic agents is the next treatment option.

Monotherapy is defined as the use of a single oral hypoglycemic agent. Combination therapy is defined as the use of two or more oral hypoglycemic agents (either separate agents or in a combined formula). Multiple drug combinations are being used and several oral hypoglycemic combination agents are commercially available for ease of dosing.

Efficacy of all oral hyperglycemic agents declines with time. This may be due to any of the following reasons:

- Natural progression of the disease
- Further decline in beta cell-to-insulin secretion
- An underlying stressful disease or condition
- Person's inability to follow dietary management and physical activity regimens

Oral medications are not useful for people with Type 1 diabetes and thus insulin is the chosen mode of treating hyperglycemia for those individuals.

Insulin

Insulin is mandatory for the treatment of Type 1 diabetes. Likewise, many people with Type 2 diabetes will require insulin to help achieve optimal glucose control. Average daily insulin requirements are 0.7 units/kg for people with Type 1 diabetes and 1.0 unit/kg for people with Type 2 diabetes. Intensive insulin regimens include pre-meal administration of a rapid or short-acting insulin, such as Aspart (Novolog), Lispro (Humalog), Glulisine (Apidra), or Regular and once daily basal insulin, such as Glargine (Lantus). Continuous subcutaneous insulin infusion (CSII) via insulin pump may also be used. Other commonly used regimens include rapid or short acting insulin plus intermediate acting insulin at breakfast, rapid or short acting insulin at supper, and intermediate insulin (NPH) at bedtime. Intermediate (NPH) or long acting (Lantus) insulin can also be used once a day in combination with oral agents for people with Type 2 diabetes.

Hypoglycemia

Most diabetes medications/insulin can cause hypoglycemia. Hypoglycemia is low blood glucose sugar (*less than 70 mg/dL*) and can be caused by all of the following:

- Skipping meal, delaying meals, or not eating enough at meals.
- Eating too little, or less than usual.
- Increased physical activity.
- Ingesting alcohol without eating.
- Taking too much insulin or other glucose lowering medications.
- Taking oral medications or injecting insulin too soon before eating.
- Taking rapid acting insulin (Humalog or Novolog) before a meal (when blood sugar level is lower than usual).

Signs and symptoms of low blood sugar may vary from person to person and include the following: shaking/trembling, sweating, pounding heart, fast pulse, tingling in extremities, numbness around lips, blurred vision, slurred speech, dizziness, and hunger. People who lack early warning signs and symptoms may have hypoglycemia unawareness and need to have their glycemic goals and treatment plan modified. Children and the elderly may also require modification of their glycemic goals due to safety concerns.

Blood glucose testing is recommended before, during, and after any potentially dangerous activity, as mild hypoglycemia can impair a person's ability to:

- operate motorized or moving vehicles (e.g., automobile, motorcycle, lawn mower, scooter, bike)
- operate equipment or machinery (e.g., power tools, firearms)
- be alert to potential dangers during physical activities (e.g., swimming, diving, skiing)

A glucagon kit is recommended for any person using insulin. Glucagon is used for the treatment of severe hypoglycemia (when the individual requires assistance from another person) and must be injected subcutaneously. Glucagon is necessary if a person is unconscious or uncooperative or can not take oral glucose gel or fluids. Emergency identification is also recommended for anyone taking oral hypoglycemic agents and/or insulin.

Moreover, overtreating low blood sugar levels with an inappropriate carbohydrate source, such as a candy bar, is common and may cause significant rebound hyperglycemia. The "Rule of 15" is safe and effective for treating low blood glucose (see Table 8).

Table 8: Treatment of Hypoglycemia – Rule of 15

- 1) Give a 15 gram carbohydrate oral feeding of one of the following:
 - 8 oz of low fat/non-fat milk
 - 4 oz of any juice without sugar added
 - 4 oz of regular soda pop
 - 1 tube of glucose gel
 - 3 glucose tablets
- 2) Wait 15 minutes. Recheck blood glucose. If still less than 70 mg/dL, repeat 15 gram carbohydrate oral feeding.
- 3) Continue to recheck blood glucose every 15 minutes and repeat “Rule of 15” as necessary until no longer hypoglycemic.
- 4) Always troubleshoot for the cause of the hypoglycemic episode. Too much medication, extra activity, medication taken/given at wrong time, or delaying a meal are common reasons for hypoglycemic episodes.

** If, after a hypoglycemic episode, a meal is not anticipated or possible, it is beneficial to eat a small protein snack to help sustain blood sugar.

Sick-Day Management

During illness, the body releases stress hormones that oppose the action of insulin, and contribute to hyperglycemia and the formation and accumulation of ketones. Any person with diabetes who is ill, is at higher risk of dehydration and ketosis or hyperosmolar hyperglycemic state (HHS), and hospitalization may be required. Other circumstances such as surgery, infection, injury, emotional trauma, and even certain medications can cause physiological stress, leading to hyperglycemia. Managing diabetes during illness may require special care to achieve and maintain euglycemia, maintain fluid and electrolyte balance, provide adequate nutrition, and prevent further complications. Sick-day management is a survival skill and all people with diabetes will require detailed sick-day instructions.

Referral to Diabetes Specialist

A diabetologist, endocrinologist, or other health care provider specializing in diabetes may be necessary to assist in optimizing glycemic control. Consider a referral to an endocrinologist for all people with Type 1 diabetes; however, people with Type 2 diabetes may benefit as well.

Essential Patient Education for Glycemic Control

The person with diabetes has the primary responsibility of improving and maintaining glycemic control and setting personal goals. Educational strategies should take into consideration special educational and cultural needs and literacy level/skill, while respecting the individual’s willingness to change behavior. Education may include, but is not limited to, the following:

- Reinforce the benefits of healthy eating, weight reduction (if needed), and physical activity.
- Discuss benefits of excellent glycemic control.
- Provide reminders that oral medication and/or insulin are helpful in lowering blood sugars, but that dietary choices and physical activity are equally important.

- Instruct in self-monitoring of blood glucose (SMBG), evaluate technique and accuracy of monitoring, provide guidance for testing times, and show how this data can be used to determine and justify necessary treatment or therapy changes.
- Offer positive reinforcement for self-care behaviors, such as frequent SMBG, data collection, and healthy eating.
- Discuss importance of developing a creative self-management regimen that will work best for the individual's lifestyle.
- Assist person in identifying personal goals that are realistic and obtainable.
- Teach problem-solving strategies in order to meet day-to-day care goals.
- Provide guidelines for prevention and treatment of hypoglycemia, as treatment regimens change and intensify; provide sick-day guidelines.
- Explain and share information to enhance understanding of A1c.
- Remind of the importance of A1c testing every 3-6 months, other regular care screenings, and follow-ups.

Helpful Tools Included in This Section

- Algorithm 1 – Type 2 Diabetes: Glycemic Control
- Diabetes Medications Update – 2004
- Insulin 2004
- Diabetes Sick Days Plan

Glycemic Control – Question and Answer

Q: What is a fructosamine test and is this lab test acceptable for monitoring long-term glycemic control?

A: A fructosamine test, or glycated serum protein test, reflects changes in glycemic control over a period of one or two weeks. A fructosamine test may be useful for detecting more short-term changes in glycemic control and assessing control where an A1c test may not be accurate (hemolytic anemia, erythropoietin therapy, and hemoglobinopathies). It may also be useful in situations where information on the last two weeks of glycemic control is required. Measurement of a fructosamine level, however, has not been demonstrated to correlate with the risk of development of complications and thus should not be considered equivalent to an A1c test.

Q: Who should consider an insulin pump?

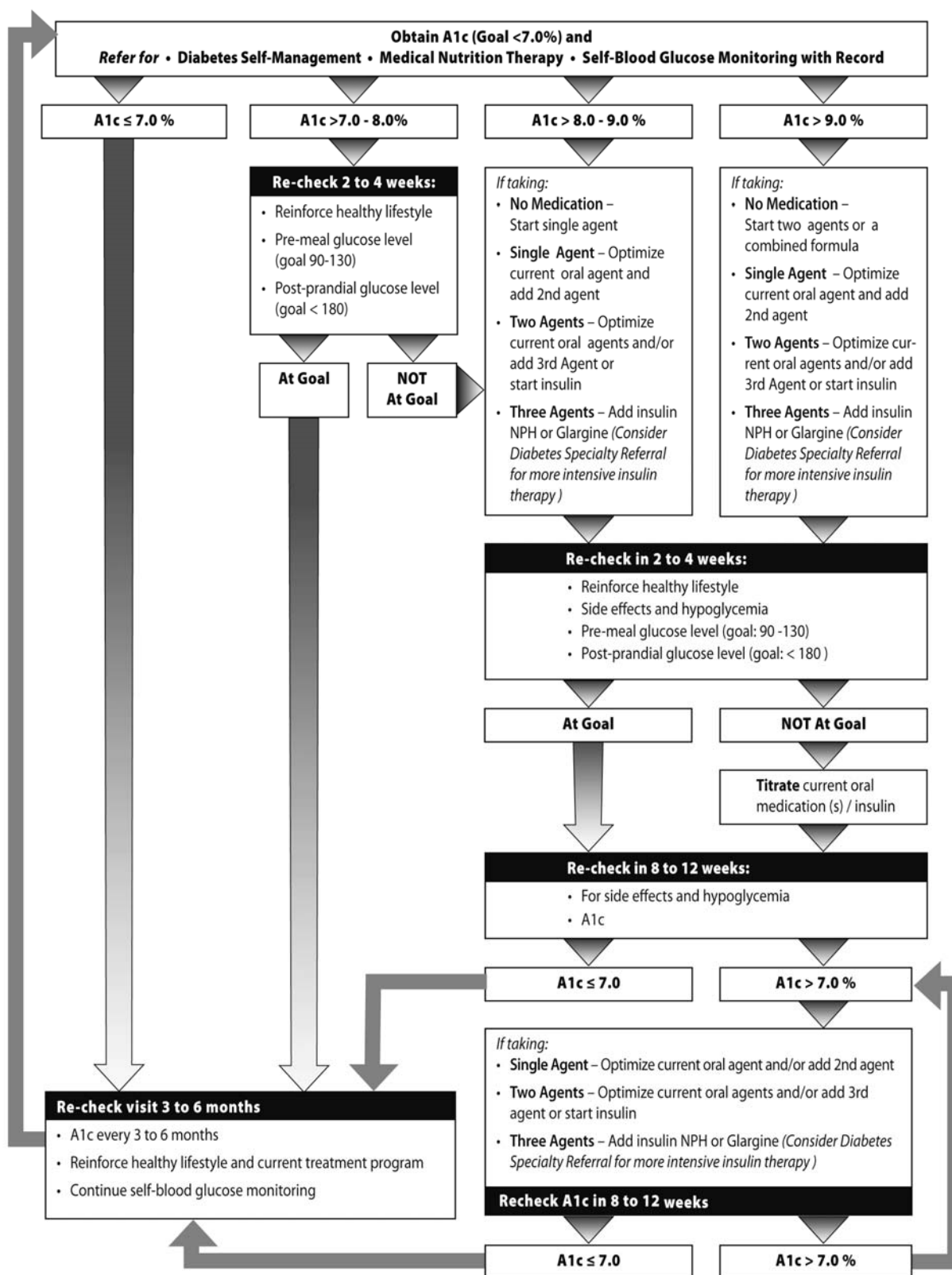
A: People with Type 1 and Type 2 diabetes may be candidates for pump therapy. People who might consider using a pump usually share some of the following characteristics:

- Take three or more insulin shots per day.
- Experience frustration and/or are tired of multiple injections.
- Are interested in improving their glucose control.
- Experience frequent hypoglycemia or have hypoglycemia unawareness.
- Express interest in more flexibility and convenience.
- Are willing to invest time and energy into learning a new insulin delivery approach and are able to fulfill follow-up responsibilities.

References

- 1) The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
- 2) UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet*. 1998;352:837-853.
- 3) Klonoff DC, Schwartz DM. An economic analysis of interventions for diabetes. *Diabetes Care*. 2000;23:390-404.
- 4) Moss SE, Klein R, Klein BE. Risk factors for hospitalization in people with diabetes. *Arch Intern Med*. 1999;159:2053-2057.
- 5) Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA*. 1998;280:1490-1496.
- 6) American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2004;27:S15-S35.
- 7) Braunstein SN, Combs P, Campbell RK. Optimal glycemic control with insulin therapy: lowering A1c and raising standards. Highlights of a symposium held at the 30th Annual Meeting and Exhibition of the American Association of Diabetes Educators on August 6, 2003. Supplement to *The Diabetes Educator*.
- 8) Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA*. 2004;291:335-342.
- 9) Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with Metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern Med*. 2003;163:2594-2602.
- 10) Warshaw HS. Referral to diabetes self-management training and medical nutrition therapy: why now and how? *Practical Diabetology*. 2004; 12-19.
- 11) Wyne KL. The need for reappraisal of type 2 diabetes mellitus management. *Type 2 Diabetes Management: A Postgraduate Med. Special Report*. 2003:5-14.
- 12) Bloomgarden ZT. Treatment of type 2 diabetes: the American Association of Clinical Endocrinologists Meeting, May 2002. *Diabetes Care*. 2002;25:1644-1649.
- 13) Nathan DM. Clinical review 146: The impact of clinical trials on the treatment of diabetes mellitus. *J Clin Endocrinol Metab*. 2002;87:1929-1937.
- 14) CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *JAMA*. 2002;287:2542-2551.
- 15) Hanefeld M, Brunetti P, Schernthaner GH, Matthews DR, Charbonnel BH for the QUARTET Study Group. One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. *Diabetes Care*. 2004;27:141-147.
- 16) Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA*. 2002;287:2563-2569.
- 17) Homko C, Deluzio A, Jimenez C, Kolaczynski JW, Boden G. Comparison of insulin aspart and lispro: pharmacokinetic and metabolic effects. *Diabetes Care*. 2003;26:2027-2031.
- 18) Parnes BL, Main DS, Dickinson LM, et al. for CaReNet and HPRN. Clinical decisions regarding HbA1c results in primary care: a report from CaReNet and HPRN. *Diabetes Care*. 2004;27:13-16.
- 19) Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. *Diabetes Care*. 2002;25:275-278.
- 20) Funnell MM, Kruger DF. Type 2 diabetes: treat to target. *Nurse Pract*. 2004;29:11-23.
- 21) DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA*. 2003;289:2254-2264.
- 22) Wyne KL, Drexler AJ, Miller JL, Bell DS, Braunstein S, Nuckolls JG. Constructing an algorithm for managing type 2 diabetes: focus on role of the thiazolidinediones. *Postgrad Med. Special Report*. 2003:63-72.

Algorithm 1

TYPE 2 DIABETES: GLYCEMIC CONTROL

DIABETES MEDICATIONS UPDATE – 2004

By: University of Wisconsin Diabetes Clinical Quality Coordinating Committee

I. GLUCOSE-LOWERING AGENTS						
Drug Class Cost	Sulfonylureas \$	Biguanides \$\$	Combination Products \$\$\$-\$\$\$	Meglitinides \$\$\$	α -glucosidase Inhibitors \$\$\$	TZD (Thiazolidinediones) \$\$\$\$\$
Formulary Medications	glipizide glipizide ER glyburide glimepiride (Amaryl)	metformin metformin ER metformin XR (Glucophage XR)	glyburide/metformin (Glucovance) glipizide/metformin (Metaglip) rosiglitazone/metformin (Avandamet)	repaglinide (Prandin) nateglinide (Starlix)	acarbose (Precose) miglitol (Glyset)	pioglitazone (Actos) rosiglitazone (Avandia)
Actions	<ul style="list-style-type: none"> Stimulates insulin secretion 	<ul style="list-style-type: none"> Targets hepatic cells Decreases hepatic glucose production Does not stimulate insulin secretion 	See components	<ul style="list-style-type: none"> Augments glucose induced insulin output More rapid onset of effect and shorter duration of action than sulfonylureas 	<ul style="list-style-type: none"> Slows absorption of carbohydrates Reduces post-prandial blood sugar 	<ul style="list-style-type: none"> Regulates insulin responsive genes necessary for glucose and lipid metabolism Improves sensitivity to insulin in skeletal and adipose tissue
Indications	<ul style="list-style-type: none"> Type 2 DM as monotherapy or in combination with insulin, metformin, or TZDs 	<ul style="list-style-type: none"> Type 2 DM alone or in combination with sulfonylurea or insulin Overweight Dyslipidemic Children (Glucophage is approved for pediatric patients ≥ 10 years) 	<ul style="list-style-type: none"> Type 2 DM in patients who have failed initial treatment with individual components Glucovance may be used in combination with TZDs 	<ul style="list-style-type: none"> Type 2 DM alone or in combination with metformin Prandin may be used in combination with TZDs Sulfa-allergic pts. Hypoglycemia on low doses of sulfonylureas 	<ul style="list-style-type: none"> Type 2 DM alone or in combination with a sulfonylurea. Precose may be used in combination with metformin or insulin Post-prandial hyperglycemia 	<ul style="list-style-type: none"> Type 2 DM with failed conventional oral therapy Actos and Avandia both indicated for concurrent use with metformin, sulfonylureas, insulin and as monotherapy
Contraindications	<ul style="list-style-type: none"> Use with CAUTION in sulfa-allergic patients Use caution with renal or hepatic insufficiency 	<ul style="list-style-type: none"> Do not use with renal or hepatic insufficiency CHF Excessive alcohol intake Over age 80 Acetazolamide 	See components	<ul style="list-style-type: none"> Use caution with renal or hepatic insufficiency 	<ul style="list-style-type: none"> Chronic intestinal disease Renal dysfunction (creatinine > 2.0) Cirrhosis (acarbose) 	<ul style="list-style-type: none"> CHF III & IV; Abnormal LFTs
Common Side Effects	Hypoglycemia and weight gain	Diarrhea, nausea, abdominal bloating, anorexia	See components	Hypoglycemia and weight gain	Flatulence, diarrhea, abdominal pain (less severe if titrated slowly)	Weight gain, fluid retention
Lab Monitoring	None	Baseline creatinine❖, LFTS	See components	None	Acarbose: LFTs every 3 months during 1 st year, then annually Miglitol: none	LFTs every 2 months x 1 yr, then prn (ALT)
Usual Dose	Glip: 5-20 mg bid Glyb: 1.25-20 mg qd/bid Glim: 1-4 mg qd	M: 500 mg-1000 mg bid or 850 mg qd-bid MXR: 500 mg-2000 mg qd	G: 2.5 mg/500 mg or 5 mg/500 mg bid M: Same as above A: Same as dose of each drug as monotherapy	R: 0.5 mg-2 mg w/ each meal N: 60 mg-120mg tid w/ each meal	A: 25 mg-100 mg tid M: 25 mg-100 mg tid	Pioglitazone: 15-45 mg qd Rosiglitazone: 4-8 mg qd/bid
Maximum Daily Dose	Glip: 40 mg qd Glyb: 20 mg qd Glim: 8 mg qd	M: 2550 mg qd MXR: 2000 mg qd	G: 20 mg/2000 mg qd M: 20 mg/2000 mg qd A: 8/2000 mg qd	R: 4 mg qid N: 120 mg tid	A: 100 mg tid M: 100 mg tid	Pioglitazone: 45 mg qd Rosiglitazone: 8 mg qd
AWP* (30 day supply)	Glip: \$11 – \$20 Glyb: \$7 – \$48 Glim: \$10 – \$56	M: \$33 – \$65 MXR: \$20 – \$80	G: \$50 – \$100 M: \$60 – \$120 A: \$95 – \$180	R: \$87 M: \$90	Acarbose: \$56 – \$67 Miglitol: \$42 – \$67	Pioglitazone: \$90 – \$160 Rosiglitazone: \$78 – \$136

❖ For patients under the age of 70, serum creatinine should be ≤ 1.4 mg/dL for women and ≤ 1.5 mg/dL for men.

* This is the average price wholesale. Actual prices for self-payers are higher. Due to contracting and other factors, the relative prices of products to different HMOs may differ considerably. Payment varies by payer and pharmacy.

II. INSULINS									
Formulary Medications	Lispro (Humalog – H) Aspart (Novolog) Glulisine (Apidra)	Regular (R)	NPH (N) Lente	Ultralente (UL)	Glargine (Lantus)	70/30 (N/R)	70/30 Novolog Mix (aspart protamine/ aspart)	75/25 (Humalog N/H)	50/50 (N/R)
Activity/Action • Onset • Peak • Duration	5-15" 1-2 hours 3-4 hours	30-60" 2-4 hours 6-10 hours	1-2 hours 4-8 hours 10-20 hours	2-4 hours Unpredictable 16-20 hours	1-2 hours Flat ~24 hours	30" Variable 12 hours	10-20" 1-4 hours 15-18 hours	0-15" Variable 15-18 hours	30" Variable 12 hours
Indications	Insulin is indicated in Type 2 diabetes that cannot be adequately or safely controlled with oral medications in combination with diet and physical activity. Insulin is the therapy of choice during pregnancy. Insulin can be used in conjunction with oral medications in Type 2 diabetes.								
Contraindications/ Cautions	Hypoglycemic unawareness can occur in setting of frequent hypoglycemia and rarely with use of β -blocker therapy. Glargine cannot be mixed with other insulins in the same syringe. UL may have an unpredictable peak and duration.								
Side Effects	Hypoglycemia <ul style="list-style-type: none"> May occur quickly with Lispro or Aspart Unpredictable in patients with gastroparesis May occur more frequently in patients with renal insufficiency and concomitant use of alcohol. Weight gain								
Dosing Guidelines	Type 1: Average dose is 0.4-0.8 u/kg body weight per 24 hours. This can be divided in a variety of intensive insulin regimens. Type 2: Average dose is 1-1.5 u/kg per 24 hours. If adding N at HS to oral medications, divide weight (in kg) by 4 to get dose. Insulin therapy should be modified based on home glucose monitoring and A1c levels.								
	Lispro (Humalog – H) Aspart (Novolog) Glulisine (Apidra)	Regular (R) (Humulin R/ Novolin R)	NPH (N) Lente (Humulin or Novolin)	Ultralente (UL)	Glargine (Lantus)	70/30 (N/R) (Humulin/ Novolin)	70/30 Novolog Mix	75/25 (Humalog N/H)	50/50 (N/R)
AWP/1000Units* • Vial • Cartridge • Disposable Syringe	\$70 \$94/\$86 \$90	\$31 \$64 Novolin \$43 InnoLet	\$31 \$64 Novolin \$54 Humulin \$43 InnoLet	\$31	\$61	\$31 \$64 Novolin \$54 Humulin \$43 InnoLet	\$70 \$87 \$90	\$70 \$90	\$31

* This is the average price wholesale. Actual prices for self-payers are higher. Due to contracting and other factors, the relative prices of products to different HMOs may differ considerably. Payment varies by payer and pharmacy.

III. ANTIHYPERTENSIVES								
Drug Class/Cost	ACE (Angiotensin Converting Enzyme) Inhibitors \$\$							ARB (Angiotensin Receptor Blockers) \$\$\$\$
Formulary Medications	benazepril (generic)	enalapril (generic)	captopril (generic)	lisinopril (generic)	perindopril (Aceon)	quinapril (Accupril)	trandolapril (Mavik)	losartan (Cozaar) valsartan (Diovan) olmesartan (Benicar)
Indications	<ul style="list-style-type: none"> First line agent in diabetes Hypertension Treatment of congestive heart failure Microalbuminuria (with or without hypertension) Can be used 24 hours after myocardial infarction 							<ul style="list-style-type: none"> 2nd line treatment for HTN when ACEI have failed or are not tolerated CHF – Diovan L VH – Cozaar Nephropathy – Cozaar
Contraindication	<ul style="list-style-type: none"> History of angioedema related to previous treatment with an ACEI Pregnancy or women of childbearing age not using contraception Volume depleted patients 							<ul style="list-style-type: none"> Hypersensitivity to any component Volume depleted patients
Common Side Effects	<ul style="list-style-type: none"> Cough Headaches, dizziness, fatigue, nausea, anxiety, insomnia, constipation Angioedema 							<ul style="list-style-type: none"> Similar to placebo Rare angioedema
Drug Interactions	<ul style="list-style-type: none"> Antacids: decrease effect of ACEI NSAIDs: decrease effect of ACEI Phenothiazines: increase effect of ACEI Allopurinol: increase likeliness of allergic reaction to allopurinol Digoxin: increase plasma levels of Digoxin Lithium: increase serum lithium levels, may cause toxicity Potassium and Potassium-sparing diuretics: increased potassium levels 							<ul style="list-style-type: none"> Fluconazole increases losartan serum levels
Lab Monitoring	<ul style="list-style-type: none"> Periodic serum creatinine and electrolytes Periodic WBC 							Periodic serum creatinine
	benazepril (generic)	enalapril (generic)	captopril (generic)	lisinopril (generic)	perindopril (Aceon)	quinapril (Accupril)	trandolapril (Mavik)	losartan – (Cozaar) valsartan – (Diovan) olmesartan – (Benicar)
Usual Dose	20-40 mg qd-bid	10-40 mg daily (qd or bid)	25-150 mg bid-tid	20-40 mg qd	4-8 mg qd	20-80 mg qd	2-4 mg qd	C: 50-100 mg daily (qd or bid) D: 80-160 mg (qd) B: 20 mg (qd or bid)
Maximum Daily Dose	80 mg qd	40 mg qd	150 mg tid	80 mg qd	16 mg qd	80 mg qd	8 mg qd	C: 100 mg qd D: 320mg qd B: 40 mg
Dose Strengths	5, 10, 20, 40 mg	2.5, 5, 10, 20 mg	12.5, 25, 50, 100 mg	2.5, 5, 10, 20, 40 mg	2, 4, 8 mg	5,10, 20, 40 mg	1, 2, 4 mg	C: 25, 50, 100 mg tab D: 40, 80, 160, 320 mg tab B: 5, 20, 40 mg tab
AWP/30 day Supply *	\$30 – \$60	\$10 – \$20	\$5 – \$20	\$17 – \$30	\$35 – \$49	\$36 – \$70	\$30	C: \$42 – \$58 B: \$43 D: \$47 – \$62

* This is the average price wholesale. Actual prices for self-payers are higher. Due to contracting and other factors, the relative prices of products to different HMOs may differ considerably. Payment varies by payer and pharmacy.

IV. DYSLIPIDEMIC AGENTS					
Drug Class/Cost	HMG CoA Inhibitors (statins) \$-\$\$\$\$	Cholesterol Absorption Inhibitor \$	Nicotinic Acid \$-\$	Fibrates \$	Bile Acid Sequestrants \$
Medications	lovastatin (generic) fluvastatin (Lescol, XL) simvastatin (Zocor) atorvastatin (Lipitor)	ezetimibe (Zetia)	crystalline niacin (generic) sustained release niacin (Niaspan)	gemfibrozil (generic) fenofibrate (Lofibra) (Tricor)	colestipol (Colestid) cholestyramine
Physiologic outcomes • LDL • HDL • Triglycerides	↓ 20-50% ↑ 5-15% ↓ 10-30%	↓ 17-18% alone ↓ 21% in addition to statin ↑ 2% ↓ 4-11%	↓ 10-25% ↑ 15-35% ↓ 20-50%	↓ 10-15% (may ↑ in pts w/ trig) ↑ 10-15% ↓ 20-50%	↓ 15-30% ↑ 3-5% None or ↑
Indications	Lower LDL cholesterol in patients with CHD, multiple risk factors, or very high LDL	Effective in combination with a statin for patients who can not reach goal on statin alone or who have contraindication to a statin.	Effective for moderate ↑ LDL, high TG, and low HDL	TG > 400 mg/dL	Effective for moderate LDL elevation with normal TG
Contraindications • Absolute • Relative	Active or chronic liver disease Concomitant use fibric acid derivatives, pregnancy	Same as statin when used in combination Same as statin when used in combination	Chronic liver disease, pregnancy, peptic ulcer disease Type 2 diabetes, severe gout, hyperuricemia, active gallbladder disease	Pregnancy Liver or severe renal disease, cholelithiasis	Familial dysbetalipoproteinemia, TG > 500 mg/dL TG > 200 mg/dL
Common Side Effects	Well-tolerated by most, mild GI complaints, rare hepatotoxicity	Well-tolerated by most	Flushing, upper GI complaints, gout, hyperglycemia, hepatotoxicity	Well-tolerated by most, mild GI complaints, rare hepatotoxicity	Upper and lower GI complaints, ↓ absorption of other drugs
Liver enzyme monitoring	0, 3, 6 months, then q 6 month	Same as statin when used in combination	0, 3, 6 months, then q 6 month	0, 3, 6 months, then annually	None
CPK monitoring	Complaints of muscle aches/pains/cramps	Same as statin when used in combination	Complaints of muscle aches/pains/cramps	Complaints of muscle aches/pains/cramps	None
Starting Dose	lovastatin: 20 mg qd Lescol: 40 mg qd Zocor: 20-40 mg qd Lipitor: 10-20 mg qd	10 mg qd	Crystalline: 1.5-3 g Sustained-release: 1-2 g	gemfibrozil: 600 mg bid Lofibra: 67-200 mg qd Tricor: 54-160 mg qd	Cholestyramine: 4-16 g Colestipol: 5-20 g
Maximum Daily Dose	lovastatin: 80 mg qd Lescol: 80 mg qd Zocor: 80 mg qd Lipitor: 80 mg qd	10 mg qd	Crystalline: 6 g Sustained-release: 2 g	gemfibrozil: 600mg bid Lofibra: 200mg qd Tricor: 160mg qd	Cholestyramine: 24 g Colestipol: 30 g
AWP/30 day supply*	lovastatin: \$36 – \$62 Lescol: \$51 Zocor: \$70 – \$124 Lipitor: \$62 – \$95	\$67	Crystalline: \$10 Sustained-release: \$60 – \$104	gemfibrozil: \$17 Lofibra: \$25 – \$70 Tricor: \$32 – \$84	Cholestyramine: \$42 – \$130 Colestid: \$60 – \$180
Equipotent Dosing For HMG CoA Inhibitors	Lescol 40 = lovastatin 20 = Zocor 10 lovastatin 40 = Zocor 20 = Lipitor 10				

* This is the average price wholesale. Actual prices for self-payers are higher. Due to contracting and other factors, the relative prices of products to different HMOs may differ considerably. Payment varies by payer and pharmacy.

Insulin 2004

THE BASAL INSULIN/BOLUS INSULIN CONCEPT

Basal Insulin

- Suppresses glucose production between meals and overnight
- 50% of daily needs

Bolus Insulin (Mealtime or Prandial)

- Limits hyperglycemia after meals
- Immediate rise and sharp peak at 1 hour
- 10-20% of total daily insulin requirement at each meal

COMPARISON OF HUMAN INSULIN AND ANALOGUES

Insulin Preparations	Onset of Action	Peak	Duration of Action	AWP/1000 U	Basal/Bolus
Lispro (Humalog) Aspart (Novolog) Glulisine (Apidra)**	5-15 minutes	1-2 hours	3-4 hours	\$70.00	Bolus
Regular (Humulin or Novolin)	30-60 minutes	2-4 hours	6-10 hours	\$31.00	Bolus
NPH/Lente (Humulin or Novolin)	1-2 hours	4-8 hours	10-20 hours	\$31.00	Basal
Ultralente	2-4 hours	Unpredictable	16-20 hours	\$31.00	Basal
Glargine (Lantus)	1-2 hours	Flat	~24 hours	\$70.00	Basal

**AWP not available at time of distribution.

The time course of action of any insulin may vary in different individuals, or at different times in the same individual. Time periods indicated should be considered general guidelines only.

Rapid-Acting Analogues: Lispro, Aspart and Glulisine

- Convenient administration immediately prior to meals
- Faster onset of action
- Limit postprandial hyperglycemic peaks
- Shorter duration of activity (reduce late postprandial hypoglycemia and frequent late postprandial hyperglycemia)

Short-Acting Insulins: Regular

- Slow onset of action – requires administration 20-40 minutes prior to meal; risk of hypoglycemia if meal further delayed
- Mismatch with postprandial hyperglycemic peak
- Long duration of activity; potential for late postprandial hypoglycemia
- May work better in people with high insulin requirements

Intermediate-Acting Insulins: NPH, Lente and Ultralente

- Have definite peaks that can cause excessive hypoglycemia, especially at night
- Require at least 2 injections if using as basal insulin
- Best insulin to use for people on prednisone, as the action profile matches the prednisone effect well
- Ultralente may last 24 hours in some people, but often has unpredictable peaks

Long-Acting Basal Insulin: Glargine

- Once-daily dosing, as action lasts 24 hours in most people
- Usually has a peakless profile (though may have small peak at 10-12 hours in about 10% of people)
- Less nocturnal hypoglycemia compared to NPH
- Cannot mix with other insulins

COMPARISON OF PREMIXED INSULIN

Insulin Preparations	Onset of Action	Peak	Duration of Action	AWP/1000U
75/25 (N/H)	0-15 minutes	variable	15-18 hours	\$70.00
70/30 (N/R)	30 minutes	variable	12 hours	\$31.00
50/50 (N/R)	30 minutes	variable	12 hours	\$31.00
70/30 Novolog Mix	10-20 minutes	1-4 hours	15-18 hours	\$70.00

- Best used in Type 2 patients
- Can be used alone or in combination with oral agents
- Rarely appropriate in Type 1 patients

INSULIN REGIMENS

- Depends on patient characteristics – daily schedule, timing of meals, exercise, age, compliance and schedule
- Willingness to monitor and take multiple injections
- Current pattern of high and low blood glucoses
- History of hypoglycemic unawareness

UM6687-0304P

Split mixed (N/R BID)

- 2 injections per day
- inflexible – need to eat meals at consistent times with snacks to avoid hypoglycemia
- MORE hypoglycemia with this regimen when control is tight
- Does not allow for adjustments of insulin through the day

Modified Split mixed (N/R AM | R PM | N Bedtime)

- Less nocturnal hypoglycemia and better control of fasting glucose
- 3 injections per day
- Need consistent meals through the day
- Substitute rapid-acting insulin (Aspart or Lispro) for R to further decrease risk of hypoglycemia

Intensive Insulin Regimens

- Combines a basal insulin with injections of rapid-acting insulin before each meal
- Typically 3-4 injections/day
- More flexible with regard to timing of meals and activity
- Allows for frequent adjustments/corrections
- Requires frequent monitoring of glucose
- Requires intensive patient education and support

INITIATING INSULIN THERAPY

Persons with type 1 – unless there is a learning barrier, adults with newly diagnosed type 1 diabetes should be started on an intensive insulin regimen combining basal insulin with rapid-acting insulin before meals.

EXAMPLE: INTENSIVE INSULIN THERAPY (multiple injections/day)

- Calculate the total daily insulin dose as 0.5 units of insulin/kilogram body weight
- Approximately 50% of the total daily requirement should be given as basal insulin
- Use of Glargine as basal insulin is highly recommended
- The remaining 50% divided for meals

Case Example

- If the patient weighs 60kg, the total daily requirement is $60\text{kg} \times 0.5 \text{ units/kg} = 30 \text{ units}$ per day
- The basal insulin dose is $30 \text{ units} \times 50\% = 15 \text{ units}$
- The remaining 50% (15 units in this case) is divided equally for each meal
- Rapid-acting insulin Aspart (Novolog) or Lispro (Humalog) is highly recommended.
- The dose would be 5 units before each meal

Persons with type 2 - several options for starting insulin in patients with type 2 diabetes and many patient specific factors should be used to determine the best regimen.

Patient continuing oral agents - consider adding a basal insulin such as NPH or Glargine at bedtime
Typical starting dose is 10units and can be titrated every 2-3 days

Patients transitioning totally to insulin - conventional insulin regimen (split/mixed) is standard approach

- Usually use NPH and Regular (or Aspart/Lispro)
- Calculate starting insulin dose based on 0.8 units/kg body weight; if patient is on prednisone, consider starting at 1 unit/kg body weight
- Persons with type 2 usually have insulin resistance and require more insulin per kilogram of body weight

EXAMPLE: SPLIT/MIXED REGIMEN (2 injections/day)

- Calculate the total daily insulin dose as 0.8 units per kilogram body weight
- AM dose is calculated as 2/3 of the total daily requirement (with 2/3 of the AM dose given as NPH and 1/3 given as Regular/Aspart)
- Remaining 1/3 is given before the evening meal (with half of the evening dose given as NPH and half given as Regular/Aspart)

CASE EXAMPLE

- If the patient weighs 90kg, the total daily requirement is $90\text{kg} \times 0.8 \text{ units/kg} = 72 \text{ units}$ per day
- AM dose is $2/3 = 48 \text{ units}$ in the morning (divided into 32 units NPH and 16 units Regular/Aspart)
- PM dose $1/3 = 24 \text{ units}$ (divided 12 units NPH and 12 units Regular/Aspart)

The evening dose of NPH can also be given at bedtime (instead of before the evening meal). This will decrease the chance of nocturnal hypoglycemia, but will require 3 injections of insulin per day

Pregnancy – Pregnant patients requiring insulin therapy should be referred to a provider with training and expertise in caring for women during preconception and pregnancy.

Acknowledgement: Created and Distributed by the UW Health Diabetes Clinical Quality Coordinating Committee, June 04.

Diabetes Sick Days Plan

GREEN ZONE

Green Zone—All Clear

- | | |
|---|--|
| <ul style="list-style-type: none"> ■ Blood glucose within goal range of 80 to 140 mg/dl ■ Taking usual pills and/or insulin ■ Eating and drinking normally ■ No fever | <ul style="list-style-type: none"> ■ Diabetes is under control ■ Test blood glucose 4 times a day while sick ■ Continue to take your diabetes medication ■ Keep on hand: fluids with sugar (such as apple juice), fluids with salt (such as broth) |
|---|--|

YELLOW ZONE

Yellow Zone—Caution

- | | |
|--|--|
| <ul style="list-style-type: none"> ■ Glucose tests greater than 140 mg/dl more than once in 6 hours ■ Symptoms of high blood glucose are present: thirst, dry mouth, blurred vision, frequent urination ■ Nausea, vomiting or diarrhea interfere with eating and drinking ■ Fever ■ Glucose tests lower than 70 mg/dl more than once in 6 hours | <ul style="list-style-type: none"> ■ Test blood glucose at least every 4 hours and record results ■ Continue to take your diabetes pills and/or insulin ■ Drink at least 4 oz (1/2 cup) of fluids every 30 minutes ■ Fluids should be sugar-free unless blood glucose is low or you are replacing a meal with the liquids. Treat low glucose with 15 gm of carbohydrate (see other side) and retest in 15 minutes; repeat treatment every 15 minutes until glucose is between 80–140 mg/dl |
|--|--|

RED ZONE

Red Zone—Call Your Doctor

- | | |
|---|--|
| <ul style="list-style-type: none"> ■ Glucose remains above 300 mg/dl for more than 6 hours or below 70 mg/dl after repeated treatment ■ Vomiting and diarrhea for more than 6 hours ■ You are dehydrated: very dry mouth, can't urinate after 4 hours, rapid weight loss since becoming ill ■ Confusion, sleepiness, seizures | <ul style="list-style-type: none"> ■ Call your doctor _____ ■ Information to have ready: <ul style="list-style-type: none"> • Blood glucose test results • Symptoms you have had, including fever, nausea, diarrhea and vomiting • Medication you have taken, including times and doses of insulin • What you have had to eat and drink |
|---|--|

SOFT FOOD MENU TO USE DURING ILLNESS

Here is a sample menu for a 1,200 calorie exchange pattern that is useful during sick days. Most are soft foods (easy to eat) and require little preparation.

Choice/ Exchange	Food	Choice/ Exchange	Food
<u>Breakfast</u>		<u>Dinner</u>	
1 milk	1 cup skim milk	2 lean-fat meat	1 cup cottage cheese* OR tuna
2 starch/bread	1/2 cup cooked cream of wheat AND 1 slice toast	2 vegetable	1 cup vegetable juice*
		2 starch	1 English muffin OR 1 cup mashed potatoes
1 fruit	1/2 cup fruit canned in juice OR fruit juice	1 fruit	1/2 cup fruit canned in juice OR fruit juice
<u>Lunch</u>		<u>Bedtime Snack</u>	
2 medium- fat meat	2 oz American Cheese*	1 starch/bread	1/2 cup sugar-free pudding
2 vegetable	1 cup tomato juice*	1 lean-fat meat	1/4 cup cottage cheese* OR 1 oz American cheese
2 starch/bread	6 saltine crackers AND 1/4 cup sherbet	1 fruit	1/2 cup fruit canned in juice OR fruit juice
1 fruit	1/2 cup fruit juice		
<u>Mid-afternoon Snack</u>		<p><small>*Starred foods are high in salt. If you are becoming dehydrated, you need to eat or drink salty foods if you can. If you aren't very sick and you're on a low-salt diet, stick to your regular low-salt meal plan.</small></p> <p><small>Adapted from Diabetes Forecast September 1994.</small></p>	
1 starch/bread	1 cup vegetable soup OR chicken noodle soup*		

CLEAR LIQUIDS TO USE DURING ILLNESS

If your blood glucose is in the normal range (80–140 mg/dl) and you cannot tolerate soft foods, try sipping clear liquids. The following items in the amounts listed each contain 15 grams of carbohydrate.

Foods	Amount	Foods	Amount
Apple Juice	1/3 – 1/2 cup	Gatorade	1 cup
Cranberry Juice	1/3 – 1/2 cup	Pedialyte	2 1/2 cups
Regular Soda	1/2 cup	Soup (broth based)	1 cup
Regular Jell-O	1/2 cup	Popsicles	1 popsicle

Created by Dean Health Systems. B2050401